IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Goddard, et al. (as amended herein)
Appl. No.	:	10/063,510
Filed	:	May 1, 2002
For	:	SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
Examiner	:	Gary B. Nickol
Group Art Unit	:	1642

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This Declaration is being submitted to demonstrate that polypeptides which enhance TNF-α levels are therapeutically useful.

2. I am an inventor on the above-identified patent application and am familiar with the specification and prosecution history.

3. I have extensive experience in the field of the claimed invention as indicated in the attached Curriculum Vitae provided herewith as Exhibit A.

4. The claims in the above-identified application relate to polypeptides which stimulate TNF-α release from human blood.

5. Polypeptides which can be used to enhance TNF-α levels are therapeutically beneficial. As discussed in the following paragraph, as of October 29, 1997, the filing date of the earliest application to which the present application claims priority, it was known that increasing TNF-α levels by direct administration of TNF-α ameliorates several medical conditions. The same therapeutic benefits which are achieved through direct administration of TNF-α can be achieved

by indirectly increasing TNF-α levels using the claimed polypeptides, which induce the release of TNF-α.

TNF-α was originally identified as a polypeptide which had antitumor properties. (See Carswell, E.A. et al. Proc Natl. Acad. Sci. 25: 3666-3670 (1975), attached hereto as Exhibit B). The antitumor effects of TNF-α were subsequently verified and exploited in several contexts. For example, Hallahan et al. demonstrated that adenoviral vectors comprising the TNF-α gene were successful in treating tumors in animals. (See Hallahan et al., Nat. Med. 1: 786-791 (1995), attached hereto as Exhibit C). TNF-α was also shown to induce necrosis of transplanted tumors, to have cytotoxic properties, and to have anti-viral properties (See Goeddel, D.V. et al. Cold Spring Harbor Symposia on Quantitative Biology 51:597-609 (1986) attached hereto as Exhibit D). In addition, TNF-α and other cytokines were known to protect against ionizing radiation in the context of radiotherapy. (See Neta et al., J. Immunol. 140:108 (1988), attached hereto as Exhibit E).

In addition to the foregoing scientific literature relating to the therapeutic benefits associated with administering TNF-α, numerous patents which relate to the use of TNF-α as a therapeutic agent alone or in conjunction with other therapeutically active agents had issued prior to October 29, 1997, including U.S. Patent Nos.: 5,215,743 (stabilized TNF compositions); 5,059,530 (expression vectors encoding TNF); 4,894,225 (therapeutic use of TNF in conjunction with immunotoxin); 4,980,160 (therapeutic use of TNF in conjunction with non-steroidal anti-inflammatory agents); and 4,963,354 (use of TNF as an adjuvant in combination with a substance against which it is desired to raise an immune response). Each of these patents is attached hereto as Exhibits F-J.

Since the claimed polypeptides can be used stimulate release of TNF-α, thereby increasing TNF-α levels, they can achieve the same therapeutic benefits which result from direct administration of TNF-α and which are described in the foregoing references. Accordingly, polypeptides which can be used to enhance which induce the release of TNF-α levels are therapeutically useful.

6. In addition to the therapeutic benefits resulting from using the claimed polypeptides to enhance TNF-α levels discussed above, there are other therapeutic contexts in which the claimed

polypeptides can be used to achieve therapeutic benefits by decreasing TNF-α levels. As of October 29, 1997, it was known that there were several medical conditions which can be ameliorated by reducing TNF-α levels. In particular, reducing TNF-α levels has been shown to be beneficial in treating conditions such as rheumatoid arthritis and Crohn's disease. (See Palcolog, E. Mol. Pathol. 1997, 50: 225-233 (1995) and Eigler, A. et al., Immunol. Today 18:487-492(1997), attached hereto as Exhibits K and L.

In addition, prior to October 29, 1997 numerous patents which relate to the therapeutic benefits of blocking the activity of TNF-α had issued, including U.S. Patent Nos.: 5,436,154 (antibodies which bind to and neutralize TNF-α) and 5,656,272 (methods of treating Crohn's disease using chimeric antibodies against TNF-α), attached hereto as Exhibits M and N.

The claimed polypeptides can be used to generate antibodies which neutralize the activity of the polypeptides. Such antibodies can be used to achieve the therapeutic benefits resulting from reducing TNF-α levels which are described in the foregoing references. Accordingly, polypeptides which stimulate the release of TNF-α are therapeutically useful.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: 11/24/04 By: Paul Godowski

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